



Gaudino, M., Tondi, P., Benedetto, U., Milazzo, V., Flore, R., Glieca, F., Ponziani, F. R., Luciani, N., Girardi, L. N., Crea, F., & Massetti, M. (2016). Radial Artery as a Coronary Artery Bypass Conduit: 20-Year Results. *Journal of the American College of Cardiology*, 68(6), 603-610. <https://doi.org/10.1016/j.jacc.2016.05.062>

Peer reviewed version

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[10.1016/j.jacc.2016.05.062](https://doi.org/10.1016/j.jacc.2016.05.062)

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## **Twenty years results of the radial artery as a coronary artery bypass conduit.**

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Brief title: RA for CABG

No relationship with industry.

Words: 3469.

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## **Abstract**

**Background:** There is lack of evidence for the choice of the second conduit in coronary surgery. The radial artery (RA) is a possible option but few data on its very long term outcome exist.

**Objective:** To describe the twenty-year results of RA grafts used for coronary artery bypass grafting and the long term effects of RA removal on forearm circulation.

**Methods:** We report the results of the prospective 20 years follow-up of the first 100 consecutive patients who received the RA as a coronary bypass conduit at our Institution.

**Results:** Follow-up was 100% complete. There were 64 deaths, 23 (35.9%) from cardiovascular causes. Kaplan-Meier twenty years survival was 31%. Thirty-three of the 36 survivors (91.6%) underwent RA graft control at a mean of  $19.0 \pm 2.5$  years after surgery. The RA was found patent in 24 cases (84.8% patency). In the overall population patency graft probability at 10 and 20 years was  $95.1 \pm 2.7$  at both intervals for the left internal thoracic artery (ITA),  $90 \pm 3.1$  and  $65.4 \pm 7.7$  for the RA and  $71 \pm 5.3$  and  $29.4 \pm 6.4$  for the saphenous vein (SV) ( $p = .001$  for RA vs SV,  $.006$  for RA vs ITA and  $<.0001$  for ITA vs SV). When the target vessel stenosis was  $\geq 90\%$  RA patency rate was similar to that of the ITA. No patients reported hand or forearm symptoms. The diameter of the ulnar artery was increased in the operated arm ( $2.44 \pm 0.43$  mm vs  $2.01$  mm  $\pm 0.47$  mm,  $p < 0.05$ ) and correlated with the peak systolic velocity of the second palmar digital artery (Pearson's coefficient 0.621,  $p < 0.05$ ).

**Conclusion:** The 20-year patency rate of RA grafts is good and is similar to that of the ITA for  $>90\%$  target vessel stenosis. RA harvesting does not lead to hand or forearm symptoms even at a very long term follow-up.

**Abbreviations list:** CABG (coronary artery by-pass graft), ITA (internal thoracic artery), LAD (left anterior descending artery), PPDA (proper palmar digital artery), PSV (peak systolic velocity), RA (radial artery), RGEA (right gastroepiploic artery), SV (saphenous vein).

## Introduction

The radial artery (RA) is the conduit most recently introduced in coronary artery bypass (CABG) surgery, after the great saphenous vein (SV) and the internal thoracic artery (ITA) (1).

To date there is evidence that the conduit has a postoperative patency rate higher than the SV and equivalent to the right ITA, and it has been shown that its use can lead to substantial clinical advantages in selected groups of patients (2). However, the RA is relatively underused. In a recent report from the Society of Thoracic Surgery Adult Cardiac Surgery Database the RA was used in less than 6% of all primary isolated CABG in the US in the 2000-2009 period (3). One of the reason for its limited adoption is probably the fact that up to now only limited information exists on the very long-term results of the RA, with the great majority of the studies reporting a mean follow-up of less than 10 years.

In addition, previous reports (including ours) have expressed concerns about possible harm to the forearm circulation after RA harvesting (4). This has possibly further limited the adoption of the conduit among the surgical community.

In order to contribute to its diffusion we herein describe the results of the twenty-year prospective follow-up of our initial cohort of 100 patients who received a RA graft for myocardial revascularization.

## Patients and methods

The use of the RA as a coronary artery bypass conduit was started prospectively at the Catholic University of Rome in January 1993, upon approval by the local Ethic Committee (5).

For the first 100 consecutive patients we adopted a very strict follow-up protocol that included:

- yearly clinical examination
- yearly stress test or stress myocardial scintigraphy
- 1-, 5- and 10-year angiographic control
- 1-, 5- and 10-year Echo-Doppler evaluation of forearm circulation.

Results of the 1-5- and 10-year clinical and angiographic follow-up as well as detailed description of the modifications of the forearm circulation after RA removal, the effects of the calcium channels blockers therapy and the morpho-functional remodeling of the artery after implantation in the coronary circulation have been previously published (4-10)

In this report, we describes the 20-year clinical, angiographic and Echo-Doppler results of this cohort of patients.

### *Patient Population and Surgical Technique*

Preoperative clinical details are summarized in Table 1.

Details of our surgical technique have been published (5). Briefly, all the operations were performed by the same surgical team using cardiopulmonary bypass and cardioplegic arrest. The left ITA was usually used to graft the left anterior descending artery (LAD), whereas the RA was grafted to the second target vessel. The RA target vessel was a branch of the circumflex artery in 53 cases, a branch of the right coronary artery in 36 and a diagonal in 11. SV grafts usually completed the revascularization, whereas the right ITA and the gastroepiploic artery were used in a minority of cases. The RA was anastomosed to the ascending aorta in 85 patients and to the left ITA in the remaining.

Since the beginning we adopted systematic Doppler or Echo-Doppler assessment of the adequacy of collateral ulnar circulation before RA removal according to a published method (10). The RA was always harvested from the non-dominant arm and bilateral RA harvesting was never performed.

Long-term calcium channel blocker therapy (diltiazem, 120 mg/d) was prescribed for all patients for the first postoperative year. After the results of two prospective randomized trials on the argument by our group (8, 9) the calcium channel blockers therapy was abandoned and currently is not part our routine.

### *Follow-Up*

Each patient was followed up regularly at our institution 6 months after surgery and every year thereafter. At each time interval, clinical examination and Echo-Doppler evaluation of the forearm were performed, and the results of surface ECG, stress myocardial scintigraphy, 24-hour Holter monitoring, and transthoracic echocardiography were reviewed. In case of death during the follow-up all the medical and autopsy reports were reviewed for the attribution of the cause of death. For out of hospital fatalities the death certificate was requested and reviewed. Death was considered cardiac in origin when it was preceded by evidence of myocardial ischemia, heart failure or arrhythmia.

Angiographic control or (in recent years) CT-angiographic assessment was proposed to all patients at the early (1 year), mid-term (5-year), long (10-year) and very long-term (20-year) follow-up visits and at any time when there was instrumental evidence of inducible ischemia.

Angiographies were graded independently by two experienced observers using a previously described 4 grades angiographic scale (perfectly patent, patent with irregularities, stringed, occluded) (6).

### *Statistical Analysis*

Data are expressed as mean  $\pm$  standard deviation (SD). Statistical analysis was performed with an unpaired, 2-tailed t test for means or the  $\chi^2$  test for categorical variables.

Non parametric survival analysis was used to estimate survival and patency probability for the three conduits (ITA, RA, SV). Log-rank test was used to perform pairwise comparisons of patency probability for the three conduits (Therneau T (2015). A Package for Survival Analysis in S version 2.38, URL: <http://CRAN.R-project.org/package=survival>).

To account for significant number of patients who could not receive follow-up angiography at 20 years we calculated the competing risks estimates of the cumulative incidence function for graft occlusion for the 3 conduits (Bob Gray

(2014). cmprsk: Subdistribution Analysis of Competing Risks. R package version 2.2-7. <https://CRAN.R-project.org/package=cmprsk>). Subgroup analysis was conducted according to the RA target (circumflex or right coronary artery) and the RA target stenosis degree ( $\geq 90\%$  vs  $< 90\%$ ).

Adjustment for baseline characteristics was not required as each of the three conduits analyzed was used in all patients, except for nine subjects who did not receive SV graft. All analysis were conducted with R (R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>)

Spearman's coefficient correlation was used to explore the association between morphologic and hemodynamic measures at Echo-Doppler evaluation.

## Results

### Clinical results

Follow-up was 100% complete and mean follow-up time was  $20.8 \pm 1.5$  years.

During this period 64 of the 100 patients died (64%). The cause of death was non-cardiac in 41 cases and cardiac in 23 (35.9%). The causes on cardiac and non-cardiac death are summarized in Table 2. Kaplan-Meier 20-year survival curve is shown in Figure 1.

During the follow-up clinical or instrumental evidence of myocardial ischemia occurred in 79 patients, so that the 20 years ischemia-free survival was 21%.

### *20 years results*

Thirty-three of the 36 survivors (91.6%) underwent angiographic (30 patients) or angio-CT (3 cases) control at a mean of  $19.0 \pm 2.5$  years after surgery.

The main angiographic results are reported in Table 3.

The very long-term patency and perfect patency rates were 93.9% and 93.9% for the left ITA, 84.8% and 72.7% for the RA and 45.1% and 25.8% for the SV respectively ( $p = .23$  for the left ITA vs. RA comparison and  $< .001$  for both the ITA vs SV and RA vs SV comparisons).



The great majority (4/5 = 80%) of the cases of RA occlusion or string sign occurred in patients in whom the artery was anastomosed to the coronary arteries with stenosis  $\leq 90\%$ . No correlation was found between the location of the distal anastomosis (circumflex or right coronary artery) and the very long-term angiographic status (Table 4).

Table 5 shows the comparison between the 10- and 20-year angiographic studies in the 30 patients who underwent both angiographies. Two RA grafts that were perfectly patent at 10-year were found to be occluded at 20-year and two others developed some irregularity between the two controls, leading to a drop of the patency and perfect patency rate from 93.3% and 86.6% at 10 years to 86.6% and 76.6% respectively at 20 years.

### *Overall experience*

During the 20 years of the follow-up 98 of the 100 patients underwent at least one angiographic control: 9 patients underwent 1 angiographic control, 49 underwent two controls and the remaining 40 more than two.

Patency graft probability using the Kaplan-Meier method at 10 and 20 years was  $95.1 \pm 2.7$  at both intervals for the left ITA,  $90 \pm 3.1$  and  $65.4 \pm 7.7$  for the RA and  $71 \pm 5.3$  and  $29.4 \pm 6.4$  for the SV ( $p = .001$  for RA vs SV,  $.006$  for RA vs ITA and  $<.0001$  for ITA vs SV; see Figure 2).

When RA patency was considered in individual annual time frames in which postoperative angiography was performed the yearly RA patency varied from 80 to 100% (Figure 3).

The cumulative incidence of graft occlusion at 20 years was  $8.6 \pm 0.1$  for the left ITA,  $19.1 \pm 0.1$  for the RA and  $49.4 \pm 0.3$  for the SV ( $p = .001$  for RA vs SV,  $.006$  for RA vs ITA and  $<.0001$  for ITA vs SV; see Figure 4).

The severity of the stenosis of the target vessel had a major influence on graft patency. When the target vessel stenosis was  $\geq 90\%$  the patency of the RA was similar to that of the left ITA (Figure 4 and 5), whereas for less severe stenosis the angiographic outcome was more similar to that of the SV (Figure 6).

The location of the distal anastomosis on the circumflex or right coronary system did not influence RA patency (Figure 7).

### Evaluation of forearm circulation

No patients had signs of symptoms of hand ischemia during the postoperative follow-up.

Twenty-five patients underwent Echo-Doppler evaluation of the forearm circulation at a mean interval of  $17.6 \pm 2.1$  years from surgery. In the operated forearm there was a significant increase in the diameter of the ulnar artery ( $2.44 \pm 0.43$  mm vs.  $2.01 \pm 0.47$  mm:  $p < .05$ ). All others flow parameters were similar between the operated and control arm (Table 6). In the operated arm there was a significant correlation between the diameter of the ulnar artery and the PSV of the second proper palmar digital artery (Spearman's coefficient 0.621,  $p=0.41$ , Figure 8A). This correlation was absent in the control arm (Figure 8B).

## Discussion

Since the reintroduction of the conduit in coronary surgery (1), most of the morpho-functional features, biological properties and vasoreactive profile of the RA have been elucidated (11). The early and intermediate angiographic patency rates have been published (2) and this year the Radial Artery Patency and Clinical Outcome trial should report its 10-year angiographic and clinical results.

Notably, there is growing evidence that the patency rate of the RA is better than that of the SV (2). The RA contends to the right ITA for the role of the second conduit for CABG and is probably a better choice in patients at high risk of sternal complications (2, 12).

Despite that, the RA is markedly underutilized. In a recent report from the STS Adult Cardiac Surgery Database the RA was used in slightly more than 5% of all primary isolated CABG procedures performed in the US from 2000 to 2009 (3)

Possible reasons for this underuse are the lack of very long term data and concerns of accelerated atherosclerosis of the ulnar artery after RA removal (4).

To date only one group has reported a RA follow-up > 10 years. Acar and colleagues (who have the merit of the RA rediscovery in the early 90's) reported their 20-year experience in a cohort of 563 patients. At a mean follow-up of 9.2 years freedom from overall and cardiovascular death was 80.3% and 92.7% respectively. Angiographic follow-up was obtained in 351 patients at a mean interval of 7.0 years from surgery and the RA patency rate was 87.9%. In patients with the longest follow-up interval the RA patency rate was 81.4% at 13.1 years (13)

In our 20-year study the patency rate of the RA was 84.8% with a perfect patency rate of 72.7%. The status of the graft remained substantially stable in the very long term follow-up, with only 2 occlusions occurring between the 10-

and the 20-years control in the group of patients who underwent both (Table 5). As in our previous reports (2, 6) the location of the target vessel did not influence graft outcome. The circumflex and right coronary artery distributions had in fact similar RA graft patency rates (Figure 7).

Instead, confirming previous observations (14), we found a strong correlation between the severity of the target vessel stenosis and the RA patency. When the RA was used to revascularize target vessel with  $\geq 90\%$  stenosis the patency rate of the conduit was similar to that of the left ITA, whereas for lower degree of coronary stenosis the angiographic outcome was more similar to that of the SV (Figures 4-6).

The Echo-Doppler evaluation of the forearm circulation testified the development of an adequate ulnar collateral circulation several years after surgery. The great majority of flow parameters were similar between the two forearms and in the operated site there was a clear correlation between the diameter of the ulnar artery and the PSV of the second proper palmar digital artery. Most importantly, no patient had signs or symptoms of hand ischemia during the 20 years follow-up (and this is common to our overall experience in more than 1600 RA cases). The small Echo-Doppler differences reported between the operated and control arms did not have a clinical correlate and, at this point of the follow-up, are unlikely to ever have any.

On this basis, the previous concerns about a possible accelerated atherosclerosis in the ulnar artery of the operated forearm (4) seem unsubstantiated.

This is an observational prospective study and has obvious limitations related to the sample size and lack of a control group. Moreover, only few of the patients who died during the follow up had their graft imaged in the days before death and this leaves unanswered the question of the graft status at that moment and his relation with the fatal event.

The main strength of this study is the 100% complete prospective 20-year clinical and seriate angiographic follow-up. In conclusion, the 20-year clinical, angiographic and Echo-Doppler results of RA conduits used for CABG are good. The 20-year patency rate is 84.8% and the status of the artery remains stable during the very long term follow-up. The location of the target vessel does not influence graft outcome, whereas the severity of the coronary stenosis is a major determinant of patency. Finally, after harvesting of the RA the ulnar collateral circulation provides sufficient flow to the arm and clinically evident forearm or hand ischemia never occurs, even at extended follow-up.

**Perspectives.**

**Competency in Medical Knowledge :** The use of the radial artery during coronary artery bypass operations is associated with better patency rate than the saphenous vein and similar to that of internal thoracic artery when target vessel stenosis is occlusive or subocclusive

**Competence in Patient Care:** Arterial conduits appear to have better patency rates and clinical results compared to venous conduits. However, they are not routinely used in clinical practice.

**Translational Outlook:** Further research is needed to verify the early and late effect of a more systematic use of the radial artery during coronary artery bypass operations.

**Key words:** radial artery, coronary artery by-pass graft surgery ,saphenous vein, internal thoracic artery.

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## Figure legends

**Figure 1.** Long term survival and event-free survival curves

**Figure 2.** Kaplan-Meier estimate of graft patency.

**Figure 3.** Radial artery patency per annum-specific for the postoperative year in which the angiography was performed.

**Figure 4.** Risk of graft failure by competing risk analysis in the overall population and for RA grafts anastomosed to target vessel with  $\geq 90\%$  stenosis.

**Figure 5.** Kaplan-Meier estimate of graft patency for RA grafts anastomosed to target vessel with  $\geq 90\%$  stenosis.

**Figure 6.** Kaplan-Meier estimate of graft patency for RA grafts anastomosed to target vessel with  $< 90\%$  stenosis.

**Figure 7.** Radial artery patency rate according to location of the distal anastomosis.

**Figure 8.** Correlation between the diameter of the ulnar artery (UA) and the peak systolic velocity (PSV) of the second proper palmar digital artery (II PPDA) in the operated (A) and control forearm (B).